ČESKÁ ASOCIACE **INTERVENČNÍ KARDIOLOGIE**

FAKULTNÍ NEMOCNICE BRNO

Intervenční kardiologie
IKK FN Brno

Antitrombotická léčba a akutní koronární syndromy

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Sympózium ČAIK, sjezd ČKS, 15.5.2016

Deklarace konfliktu zájmů

	Nemám konflikt zájmů	Mám konflikt zájmů	Specifikace konfliktu (vyjmenujte subjekty, firmy či instituce, se kterými Vaše spolupráce může vést ke konfliktu zájmů)
Zaměstnanecký poměr	✓		
Vlastník / akcionář	✓		
Konzultant		✓	
Přednášková činnost	✓		
Člen poradních sborů (advisory boards)	✓		
Podpora výzkumu / granty	✓		
Jiné honoráře (např. za klinické studie či registry)		✓	

1. STEMI a primární PCI

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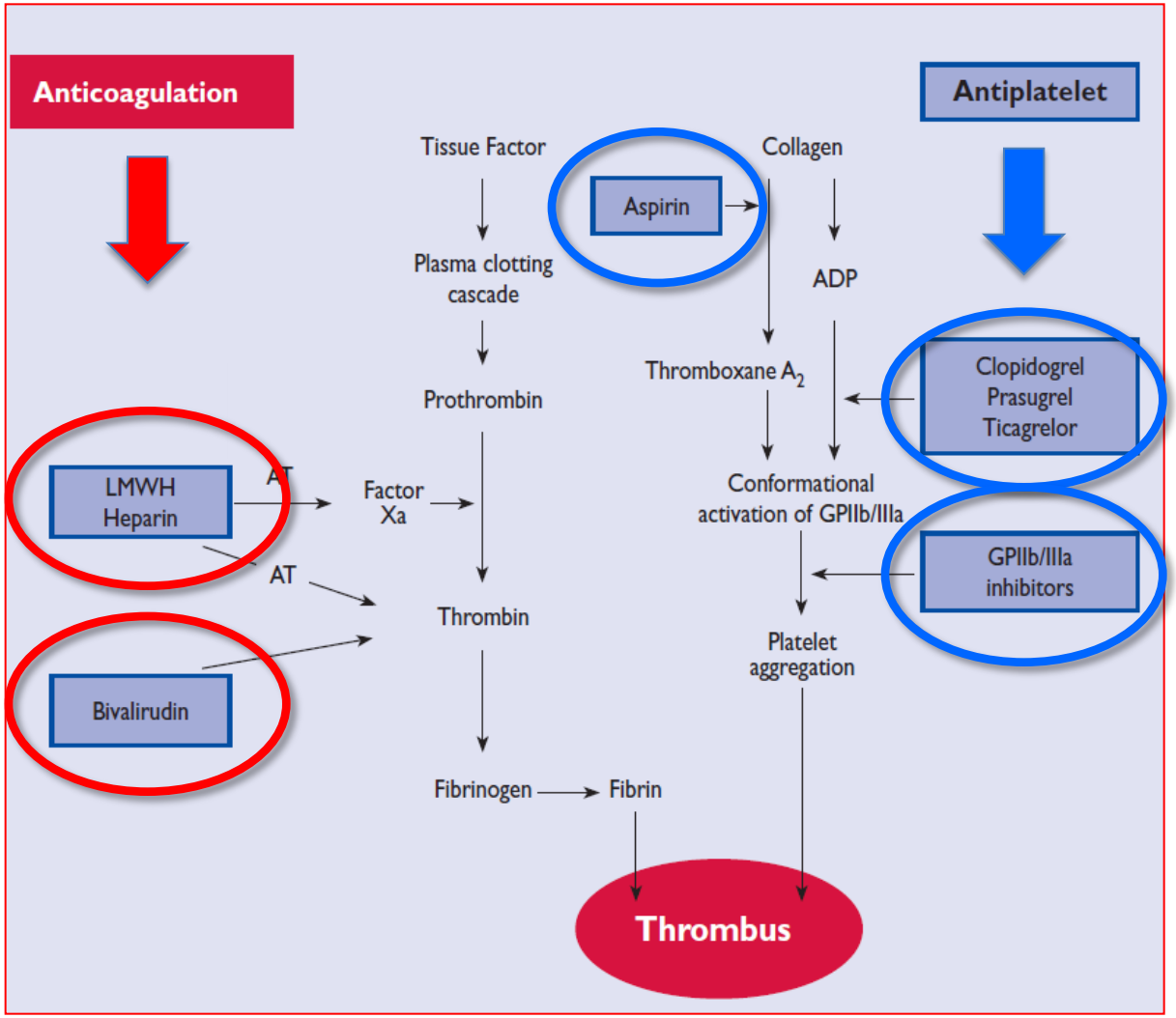
Přednemocniční **Periprocedurální** Nemocniční Dlouhodobé



Abciximab

Eptifibatide

Tirofiban

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1. Kys. acetylosalicylová

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- **Rutinní podání co nejdříve!**
  - **ESC – LD 150-300mg p.o. (80-150mg iv)**
  - **ACC – 162-325mg p.o.**

- **V případě alergie na ASA nepodávat a provést desentizaci:**
  - **Wong et al 2000**
  - **Schaefer and Gore 1999**
  - **Silberman et al 2005**

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2. P2Y12 inhibitors: Farmakokinetika a farmakodynamika

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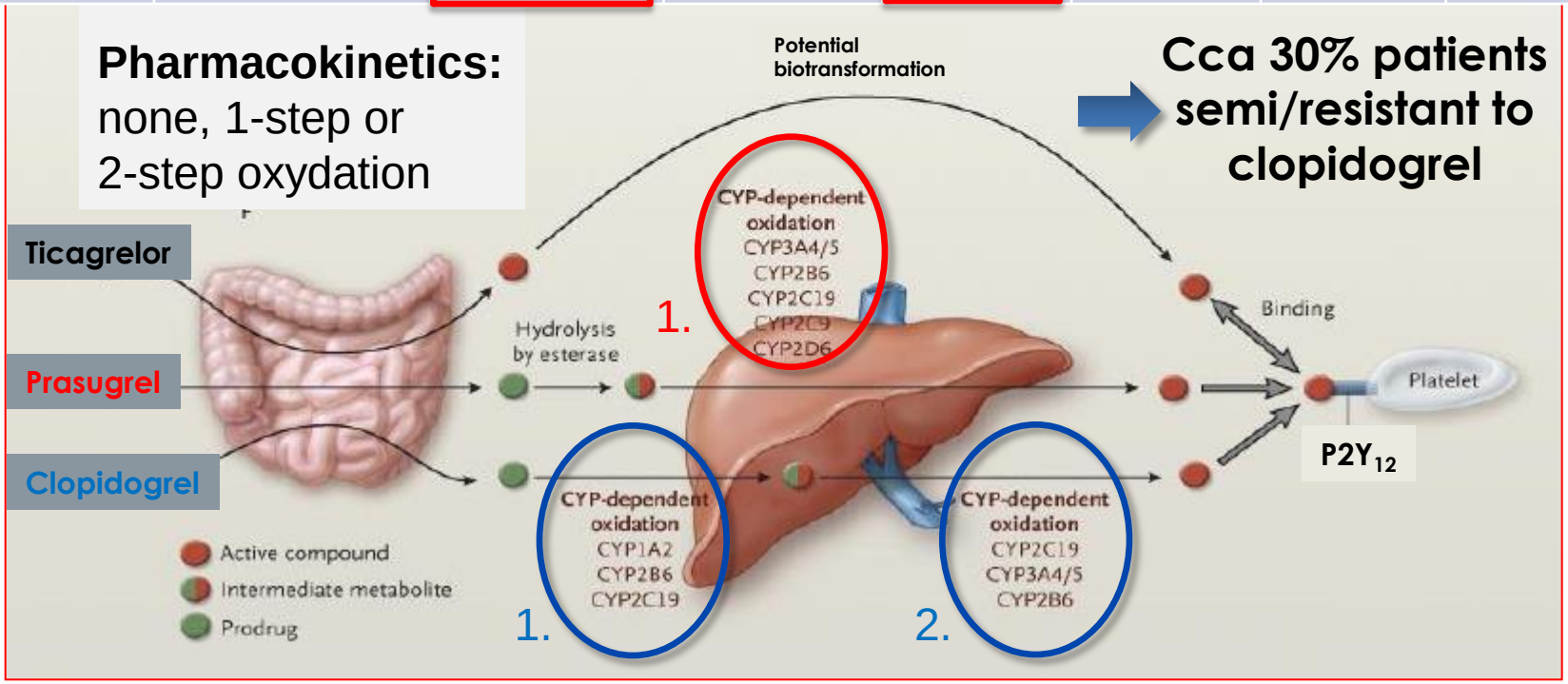
Drug	Administration	Activation (CYP dependant)	Receptor binding	Onset of action	Offset of action	Loading dose	Maintenance dose
Clopidogrel	oral	sensitive to inhibition	irreversible	2-8 hrs	7-10 days	600mg	1x75mg
Prasugrel	oral	**resistant to inhibition**	irreversible	**0,5-4 hrs**	7-10 days	60mg	1x10mg (5mg)
Ticagrelor	oral	**not needed**	reversible	**0,5-2 hrs**	3-5 days	180mg	2x90mg

Pharmacokinetics:
none, 1-step or
2-step oxydation

Cca 30% patients semi/resistant to clopidogrel



Ferreiro JL, Circ Cardiovasc Interv 2012;5:433-445

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Clopidogrel – ACS STEMI - studie

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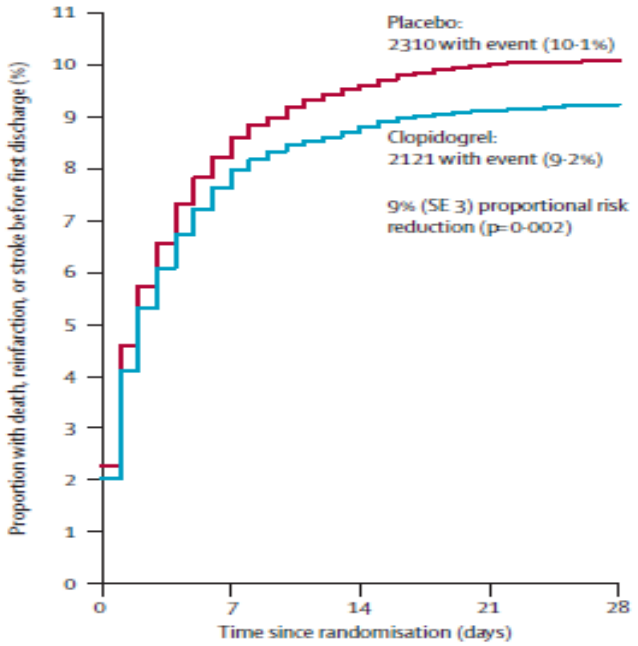
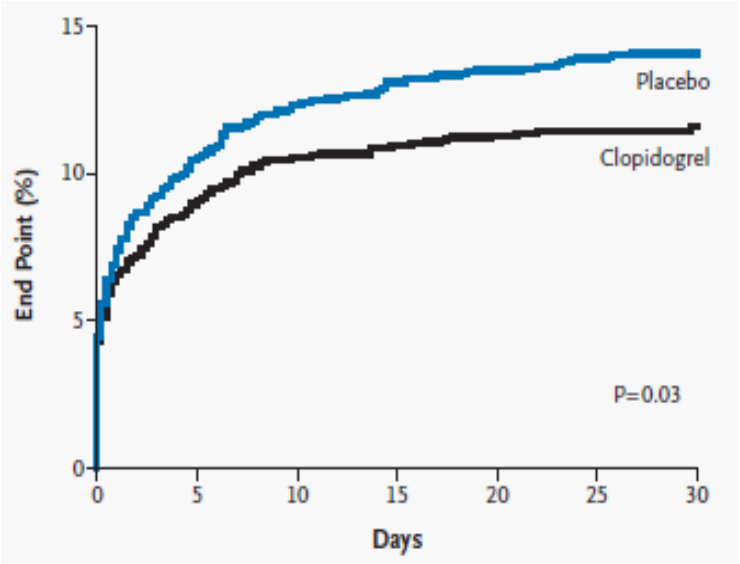
COMMIT (n=45852, 93% STEMI) – Cl 75mg + ASA vs ASA (50% FL)
CLARITY (n=3491): Cl 300 + 75mg + ASA + FL vs placebo + ASA + FL (PCI 57%)

COMMIT:
• 28days: RRR 9%↓



Commit trial. The Lancet 2005; 366: 1622–1632.

CLARITY:
• 30 days: RRR 20%↓



Clarity trial. NEngl J Med 2005; 352: 1179–1189.

!!! Ne PPCI éra !!!

Prasugrel/Ticagrelor vs Clopidogrel studie

Ticagrelor vs clopidogrel – Plato

NSTE-ACS (moderate-to-high risk) **59%**, STEMI (if primary PCI) **38%**
Clopidogrel-treated or -naïve; All patients received ASA
randomized within 24 hours
(N = 18,624)

Clopidogrel
300-mg loading dose unless pre-treated
then 75-mg once-daily maintenance;
(additional 300 mg allowed pre-PCI)
(N = 9,291)

6-12 month expos
Median 9.2 mont

Primary End Point: CV Deat
Primary Safety End Point: Toto

Wallentin L, et al. N Engl J Med 2009;361:1045-1057

Prasugrel vs clopidogrel – Triton TIMI 38

NSTE-ACS (TIMI score ≥3) **74%**
STEMI (primary PCI ≤12 hours or delayed PCI>12 hours – 14 days) **26%**
Clopidogrel-naive; All patients received ASA
randomized within 72 hours of index event
(N = 13,608)

Clopidogrel
300-mg loading dose
then 75-mg once-daily maintenance;
(N = 6,795)

Prasugrel
60-mg loading dose
then 10-mg once-daily maintenance
(N = 6,813)

6-15 month exposure
Median 14.5 months

Primary End Point: CV Death, MI, or Stroke
Primary Safety End Point: TIMI Major Bleeding

Wiviott SD, et al. *N Engl J* Med 2007;357:2001-2015

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Otázky k P2Y12 inhibitorům

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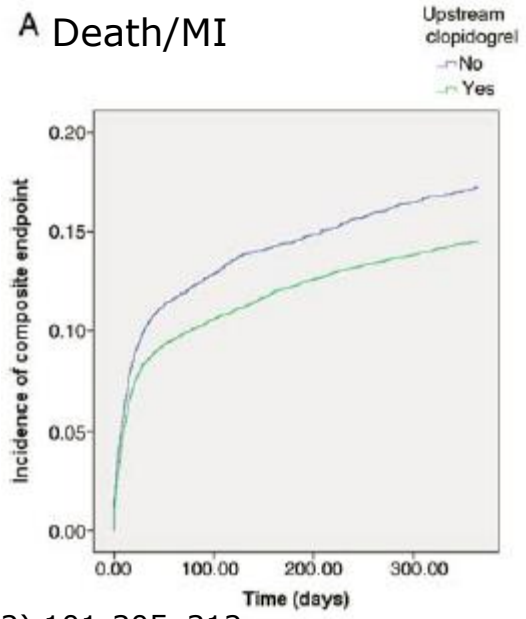
1. Podání co nejdříve (ASAP) nebo po SKG?

Atlantic study – ticagrelor v předléčené skupině:

- Trend pro častější kompletní ST rezoluce (p=0,055)
- Méně trombóz ve stentu
- Krvácení, úmrtí, CMP nebo IM – NS
- Ress: „Pretreatment is safe and might be beneficial"

Montalescot G et al. Am Heart J. 2013 Apr;165(4):515-22

CIPAMI trial with clopidogrel:
- Ress: Pretreatment with strong trends to less events, bleeding same



No randomized data for prasugrel

ASAP??

Zeymer U et al. Clin Res Cardiol (2012) 101:305–312

PRAGUE-18 (ticagrelor vs prasugrel u pacientů s AKS podstupujících emergentní PCI)

ISAR-REACT 5 study (Randomized comparison of ticagrelor versus prasugrel in patients with acute coronary syndrome and planned invasive strategy)

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3. IIb/IIIa inhibitors - indikace

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ESC guidelines 2012 = ESC guidelines (Revascul) 2014

GP IIb/IIIa inhibitors should be considered for bailout therapy if there is angiographic evidence of massive thrombus, slow or no-reflow or a thrombotic complication.	IIa	C
Routine use of a GP IIb/IIIa inhibitor as an adjunct to primary PCI performed with unfractionated heparin may be considered in patients without contraindications.	IIb	B
Upstream use of a GP IIb/IIIa inhibitor (vs. in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI.	IIb	B
Options for GP IIb/IIIa inhibitors are (with LoE for each agent):		
• Abciximab		A
• Eptifibatide (with double bolus)		B
• Tirofiban (with a high bolus dose)		B

ACC guidelines 2013

IV GP IIb/IIIa receptor antagonists in conjunction with UFH or bivalirudin in selected patients		
• Abciximab: 0.25-mg/kg IV bolus, then 0.125 mcg/kg/min (maximum 10 mcg/min)	IIa	A
• Tirofiban: (high-bolus dose): 25-mcg/kg IV bolus, then 0.15 mcg/kg/min	IIa	B
• In patients with CrCl <30 mL/min, reduce infusion by 50%		
• Eptifibatide: (double bolus): 180-mcg/kg IV bolus, then 2 mcg/kg/min; a second 180-mcg/kg bolus is administered 10 min after the first bolus	IIa	B
• Pre–catheterization laboratory administration of IV GP IIb/IIIa receptor antagonist	IIb	B
• Intracoronary abciximab 0.25-mg/kg bolus	IIb	B

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Otázky k podání GPI

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1. Pacienti předléčeni LD P2Y12 před SKG

Ano, bezpečně

On-Time (Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty)
EUROMAX (randomized open-label ambulance trial of bivalirudin versus standard-of-care anticoagulation in patients with acute ST-segment-elevation myocardial infarction transferred for PPCI)

2. Efekt IC podání s/bez následné infůze?

Možná..

Metanalysis Piccolo et al (Eurointervention 2014):

- Abciximab IC fewer death and reIM in diabetics with STEMI vs IV administration
- Trends to better angiographic results

4. Antikoagulační léčba

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ESC guidelines 2012

An injectable anticoagulant must be used in primary PCI.	I	C
Bivalirudin (with use of GP IIb/IIIa blocker restricted to b ut) is recommended over unfractionated heparin and a GP IIb/IIIa blocker.	I	B
Enoxaparin (with or without routine GP IIb/IIIa blocker) be preferred over unfractionated heparin.	IIb	B
Unfractionated heparin with or without routine GP IIb/I locker must be used in patients not receiving bivalirudin or enoxaparin.	I	C

ESC guidelines (Revascul) 2014

Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI.	I	A
The anticoagulation is selected according to both ischaemic and bleeding risks, and according to the efficacy–safety profile of the chosen agent.	I	C
Unfractionated heparin: 70–100 U/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned; 50–70 U/kg i.v. bolus with GP IIb/IIIa inhibitor.	I	C
Bivalirudin 0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/h for up to 4 hours after the procedure.	IIa	A
Enoxaparin i.v. 0.5 mg/kg with or without GP IIb/IIIa inhibitor.	IIa	B

ACC guidelines 2013

• UFH:	I	C
• With GP IIb/IIIa receptor antagonist planned: 50- to 70-U/kg IV bolus to achieve therapeutic ACT‡		
• With no GP IIb/IIIa receptor antagonist planned: 70- to 100-U/kg bolus to achieve therapeutic ACT§	I	C
• Bivalirudin: 0.75-mg/kg IV bolus, then 1.75–mg/kg/h infusion with or without prior treatment with UFH. An additional bolus of 0.3 mg/kg may be given if needed.	I	B
• Reduce infusion to 1 mg/kg/h with estimated CrCl <30 mL/min		
• Preferred over UFH with GP IIb/IIIa receptor antagonist in patients at high risk of bleeding	IIa	B

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Otázky k antikoagulační léčbě u STEMI

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1. Hledání optimální léčby pro individuálního pacienta

Table 1| **Evidence based considerations for anticoagulant choice during primary percutaneous coronary intervention for patients with ST segment elevation myocardial infarction**

Anticoagulant	2013 ACC-AHA guidelines	2014 ESC guidelines	Ranking for efficacy or safety		Considerations for current practice
			MACE	Major bleeding	
Unfractionated heparin + GPI	COR I	COR I	2nd	4th	Likely worse bleeding with newer $P2Y_{12}$ inhibitors Bleeding risk somewhat mitigated with transradial procedure
LMWH + GPI	None	COR IIa	1st	3rd	Likely worse bleeding with newer $P2Y_{12}$ inhibitors Bleeding risk somewhat mitigated with transradial procedure
Unfractionated heparin	COR I	COR I	4th	2nd	Likely improved MACE with newer $P2Y_{12}$ inhibitors but may negate bleeding advantage
Bivalirudin	COR I Preferred over unfractionated heparin + GPI in those at high risk of bleeding (COR IIa)	COR IIa	3rd	1st	Likely improved MACE with newer $P2Y_{12}$ inhibitors but may negate bleeding advantage
Fondaparinux	COR III	COR III	5th	5th	Should not be recommended based on current data

ACC-AHA = American College of Cardiology Foundation and American Heart Association. ESC = European Society of Cardiology. MACE = major adverse cardiovascular event. COR = class of recommendation. GPI= glycoprotein IIb/IIIa inhibitor. LMWH= low molecular weight heparin.

Metaanalysis and suggestions by Bangalore et al. BMJ 2014;349;g6419

2. non-STEMI

European Heart Journal Advance Access published September 11, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv320

ESC GUIDELINES

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

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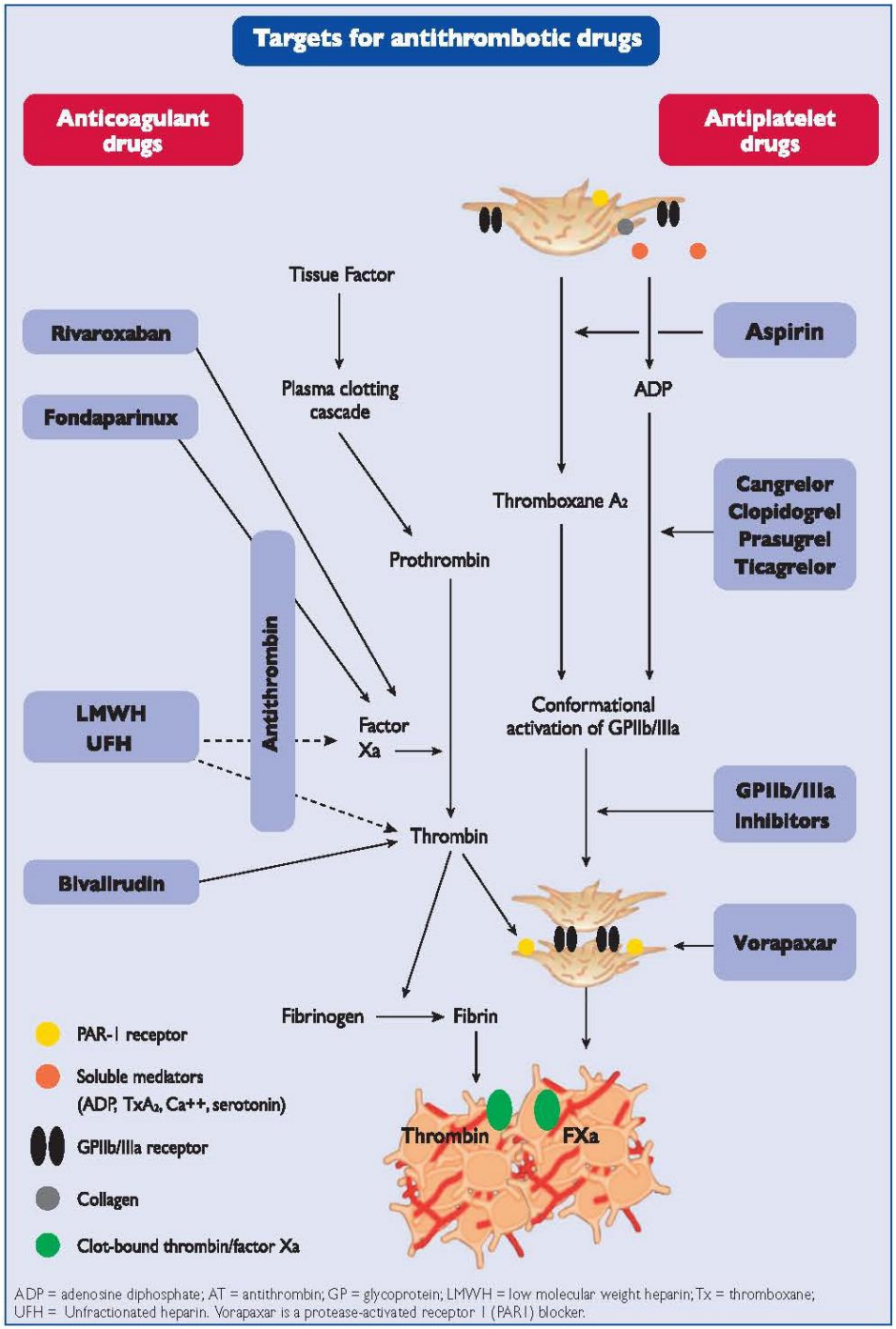
ESC entities having participated in the development of this document:

Associations: Acute Cardiovascular Care Association (ACCA), European Association for Cardiovascular Prevention & Rehabilitation (EACPR), European Association of Cardiovascular Imaging (EACVI), European Association of Percutaneous Cardiovascular Interventions (EAPCI), Heart Failure Association (HFA).

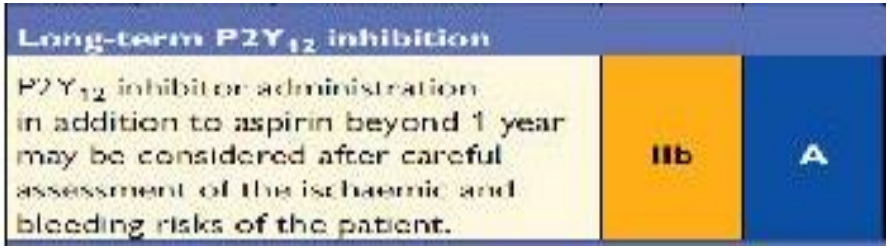
Councils: Council on Cardiovascular Nursing and Allied Professions (CCNAP), Council for Cardiology Practice (CCP), Council on Cardiovascular Primary Care (CCPC).

Working Groups: Working Group on Cardiovascular Pharmacotherapy, Working Group on Cardiovascular Surgery, Working Group on Coronary Pathophysiology and Microcirculation, Working Group on Thrombosis.



V případě, že nejsou kontraindikace, tak
1. Ticagrelor / Prasugrel
2. Clopidogrel
(LD pouze v případě dlouhého časového intervalu před katetrizací a po vyloučení indikace CABG)

selektivně



ESC Guidelines NSTE - EHJ 2015

Dosing of anticoagulants in patients with normal and impaired renal function

Drug	Recommendations		
	Normal renal function or stage 1–3 CKD (eGFR ≥30 mL/min/1.73m²)	Stage 4 CKD (eGFR 15–29 mL/min/1.73m²)	Stage 5 CKD (eGFR <15 mL/min/1.73m²)
Unfractionated heparin	• Prior to coronary angiography: 60–70 IU/kg i.v. (max 5000 IU) and infusion (12–15 IU/kg/h) (max 1000 IU/h), target aPTT 1.5–2.5x control • During PCI: 70–100 IU/kg i.v. (50–70 IU/kg if concomitant with GPIIb/IIIa inhibitors)	No dose adjustment	No dose adjustment
Enoxaparin	1 mg/kg s.c. twice a day	1 mg/kg s.c. once a day	Not recommended
Fondaparinux	2.5 mg s.c. once a day	Not recommended if eGFR <20 mL/min/1.73m²	Not recommended
Bivalirudin	Bolus 0.75 mg/kg i.v., infusion 1.75 mg/kg/h	No adjustment of bolus, reduce infusion rate to 1 mg/kg/h	adjustment of bolus, reduce infusion rate to 0.25 mg/kg/h

aPTT = activation partial thromboplastin time; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; IU = international units; i.v. = intravenous; kg = kilograms bodyweight; s.c. = subcutaneous.
Recommendations for the use of drugs listed in this table may vary depending on the exact labeling of each drug in the country where it is used.

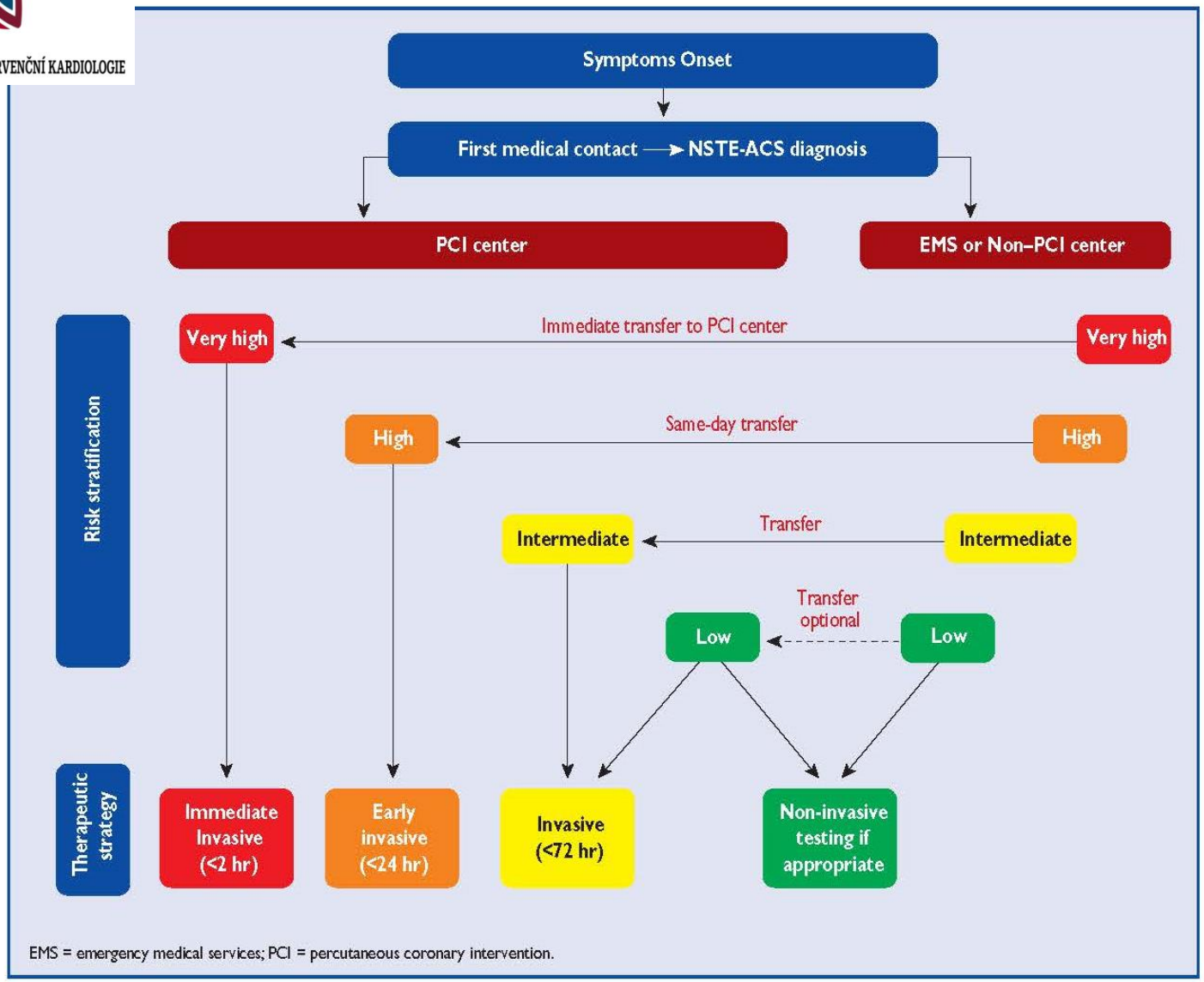


Figure 6 Selection of non-ST-elevation acute coronary syndrome (NSTE-ACS) treatment strategy and timing according to initial risk stratification.

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Závěry

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1. **STEMI = „méně" individualizovaná iniciální léčba**
    1. **Protidestičková léčba**
        1. **LD moderními P2Y12 inhibitory co nejdříve**
        2. **Selektivní podání GPI (ic vs iv s/bez infůze)**
    2. **Antikoagulační léčba**
        1. **UFH / LMWH**
        2. **Bivalirudin u pacientů s vysokým rizikem krvácení**
2. **Non-STEMI = „více" individualizovaná léčba**
    1. **Riziková stratifikace!!!**
    2. **Protidestičková léčba**
        1. **LD moderními P2Y12 inhibitory po znalosti koronární anatomie a vyloučení indikace CABG nebo v případě delší časové prodlevy do katetrizace**
        2. **Selektivní podání GPI**
    3. **Antikoagulační léčba**
        1. **UFH / LMWH**
        2. **Bivalirudin u pacientů s vysokým rizikem krvácení**
3. **Duální protidestičková léčba po dobu** 12 měsíců (nebo i déle u Ticagreloru po NSTEMI) v případě, že pacient nemá velmi vysoké riziko krvácení
    1. **Ticagrelor** u všech pacientů se střední/vysokým rizikem bez ohledu na iniciální léčbu a předléčbu Clopidogrelem (180mg/90 mg)
    2. **Prasugrel s PCI** v případě nepřítomnosti kontraindikací (60/10mg)
    3. **Clopidogrel**, když Tica/Prasu nejsou indikovány (300-600mg /75mg)
4. Prasugrel u non-STEMI není doporučen u pacientů bez znalosti koronární anatomie.